PREVENTION GENETICS
DISEASE PREVENTION THROUGH GENETIC TESTING

CLIA #: 52D1027685 ● CAP #: 7185561
AU ID: 1407125 ● NPI: 1114140571
3700 Downwind Drive
Marshfield, WI 54449 USA
Phone: 715-387-0484 Fax: 715-384-3661

Chondrodysplasia Punctata 1, X-Linked Recessive (CDPX1) via *ARSE* Gene Sequencing (Test #813)

Brief Description of Clinical Features: X-linked recessive chondrodysplasia punctata 1 (CDPX1, OMIM#302950) is characterized by abnormal cartilage and bone development, including chondrodysplasia punctata (stippled epiphyses) especially in the hands and feet, short stature, brachytelephalangy (shortening of the distal phalanges), and nasomaxillary hypoplasia. Although most affected males have minimal morbidity and skeletal findings that improve by adulthood, some have significant medical problems including respiratory compromise, cervical spine stenosis and instability, mixed conductive and sensorineural hearing loss, and abnormal cognitive development (Braverman et al. *GeneReviews* 2008).

Genetics: CDPX1 is inherited in an X-linked recessive manner. This condition is caused by a deficiency of the Golgi enzyme arylsulfatase E encoded by the *ARSE* gene. *ARSE* is located in Xp22.3, close to the pseudoautosomal boundary within a cluster of evolutionary related sulfatase genes, which encodes steroid sulfatase. These genes escape X-inactivation and have a pseudogene on the Y chromosome (Sardiello et al. *Hum Mol Genet* 14:3203–3217, 2005). The majority of disease associated mutations in the *ARSE* gene are missense and nonsense mutations, although small insertions as well as gross deletions have been reported (Nino et al. *Am J Med Genet* 146A:997–1008, 2008). In approximately 25% of individuals with features of CDPX1, routine karyotype analysis reveals Xp deletions or rearrangements that include *ARSE* (Braverman et al. *GeneReviews* 2008; Ballabio & Andria *Hum Mol Genet* 1:221-227, 1992).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons of the *ARSE* gene plus ~50 bp of flanking non-coding DNA on each side. We will also sequence any single exon (Test #100, $190) in family members of patients with a known mutation, or to confirm research results.

Reference Sequences: **Genomic: NC_000023.10** **mRNA: NM_000047.2**
Protein: NP_000038.2 **mRNA and Protein: CCDS 14122.1**

Indications for Test: Candidates for this test are patients with clinical and radiographic features consistent with CDPX1, and family members of patients who have known *ARSE* mutations.

Sensitivity of Test: Sequencing of *ARSE* is predicted to detect disease mutations in up to 75% of males who meet clinical diagnostic criteria (Franco et al. *Cell* 81:15-25, 1995; Sheffield et al. *J Med Genet* 35:1004–1008, 1998; Brunetti-Pierri et al. *Am J Med Genet* 117A:164-168, 2003; Garnier et al. *Eur J Pediatr* 166:327–31, 2007; Nino et al. *Am J Med Genet* 146A:997–1008, 2008). The failure to achieve higher mutation detection rates could reflect the inclusion of phenocopies (e.g. warfarin embryopathy, maternal vitamin K deficiency), genetic heterogeneity, or mutations in regions of *ARSE* that were not sequenced.
Note: *ARSE* gene deletions are suspected in males based on failed amplification of either the entire gene or specific exons. Those large deletions would typically not be detected in female carriers by sequence analysis.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page four of the Requisition Form.

Prices: **Sequencing of *ARSE* gene** **$ 680**

CPT Codes:

Sample Ascertainment x1	83890 $ 30	DNA Isolation x1	83891 $ 40
Amplification x10	83898 $190	Sequencing x10	83904 $280
Separation x1	83894 $ 40	Interpretation/Report x1	83912 $100

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

Contact: Dr. Ying Wang, ying.wang@preventiongenetics.com, www.preventiongenetics.com